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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,389	PEL ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3 -27 and 29-46* is/are pending in the application.

4a) Of the above claim(s) *1,3-5,16-27 and 29-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-15,33 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: three printouts of EC, IUBMB, EC2.7.8, EC 2.5, and Synthase..

The case is the national stage of the PCT/EP2003/08216. Claims 6-8,19, 29-31, 33, 40-41 have been amended; claims 2 and 28 have been cancelled, and new claims 42-46 have been added. Claims 1, 3 -27 and 29-46 are pending; claims 6-15, 33 and new claims 42-46, all reading on the elected invention are under examination.

DETAILED ACTION

Restriction/election

Applicant's election, with traverse, of Group X, claims 6-15, 33 and new claims 42-46 as related to SEQ ID NO: 5 encoding CobS protein of SEQ ID NO: 6; vectors comprising SEQ ID NO:5 and SEQ ID NO:3, or SEQ ID NO: 5 and SEQ ID NO: 3 and SEQ ID NO: 1; host cells and a method for production of vitamin B12, in the reply filed on 10/522, 389 is acknowledged. The traversal is on the ground(s) that:

1) the examination of all claims is not a serous burden;

2) the prosecution needs to be compact;

3) the public interest would be served by examination of all claims in a single application;

4) groups IX to XII share a special technical feature because they are directly or indirectly related to polynucleotides encoding for CobS taken alone or in combination with the CobU, wherein CobS and CobU are involved in the same step (i.e., final step) of vitamin B12 syntesis; and

5) cobS and cobU of P. freudenreichii are not taught by the prior art, because CobU and CobS in Table 1 of Rosner belong to Salmonella typhimurium.

Applicants' argument have been fully considered but except for argument 5) are found not persuasive for the following reasons.

Regarding arguments 1)–3) applicants are reminded that this is a 371 application in which lack of unity examined as based **on PCT Rules 13.1 and 13.2 as well as 37 CFR 1.475.** The latter does not provide for multiple products or methods within single application. The mentioned rules were used in the statement of lack of unity and election requirement mailed to Applicants on March 28, 2007. Criteria 1)-3) do not apply as a base for issuing lack of unity statement and requirement of election at the national stage of a PCT case.

Regarding point 5) the examiner accepts that Roessner does not teach cobs and cobU genes o the instant invention. Roessner teaches cobA of P. freudenreichii that gives bases for separating claims related to cobA from those directed to cobS and cobU.

Regarding point 4) the statement that proteins CobU and CobS are involved in the same, i.e. final step of vitamin B12 synthesis, is confusing and not in accord with that what is described in the application. On pages 31-36 Applicants present section D. *Uses of the disclosed polypeptides in the biosynthetic pathway and to produce witamin B12 (reaction/enzyme)* which teaches the following steps and enzymes in production of vitamine B12:

A amidation performed by amide synthase (SEQ ID NO: 2) which is encoded by cobA (SEQ ID NO:1),

B1 phosphorylation, performed by phosphotransferase (SEQ ID NO: 4)

encoded by cobU (SEQ ID NO:3)

B2 nucleotidylation performed by nucleotidyl transferase (SEQ ID NO: 4)

encoded by cobU (SEQ ID NO: 3)

C arylation, or ribazole addition, performed by aryl transferase (SEQ ID NO: 6),

encoded by cobS (SEQ ID NO:5)which leads to the final product which is vitamin B12.

D adenosylation performed by adenosyl transferase SEQ ID NO: 8 encoded by SEQ ID NO: 7 – additional pathway for precursors.

Reading this teachings one having skills concludes that CobS and CobU are not involved in the same step of synthesis, because CobU performs steps B1 and B2 and CobS performs step C. Enzymatic activities necessary for B1, B2 and C are different. Although any of the enzymes, identified as SEQ ID NOs: 2, 4, 6, and 8 participates in the metabolic pathway that leads to vitamin B12 there is no special technical feature connecting the enzymes i.e. there is lack of unity, because each of the enzyme has different enzymatic activity and there is not special technical feature. This is independent on the fact apart that cobA has been known since 1995 (Sattler et al in IDS). The reasons for lack of unity were explained in the Office Action of March 28, 2007.

Applicants elected group X related to SEQ ID NO: 5 encompassing claims 6-15, and 33. New claims 42-43 are directed to the products which are vectors comprising

SEQ ID NO: 5 and further comprising SEQ ID NO: 3 and SEQ ID NO: 1. These products comprise the elected SEQ ID NO: 5 and are reading on group X. Furthermore, host cells comprising said products, claimed by claims 44 and 45, as well as claim 46, directed to the use of the host of claim 45 reads on group X.

Currently Group X, consists of claims 6-15, 33, and 42-46. Claims 6-11, 33, 42-44 are directed to three products that are three DNA molecules (SEQ ID NO: 5 and related DNA molecules; vector comprising SEQ ID NO: 5 and further comprising SEQ ID NO:3; and vector comprising SEQ ID NO: 5 and further comprising SEQ ID NO: 3 and SEQ ID NO: 1). Claims 12-14 and 44-45 are directed to two genera of product that are host cells comprising SEQ ID NO: 5 (or related DNA molecules) and DNA molecule comprising EQ ID NO: 5 and further comprising SEQ ID NO: 3 and SEQ ID NO: 1. Claims 15 and 46 are complex method claims each directed to synthesis of three products.

In summary, the claims are directed to 5 products, and two methods of their use for production three products.

The requirement for restriction is still deemed proper and is therefore made FINAL.

Priority

Applicants claim of benefits of EPO patent application 02255203.8 filed May 2, 2003 has been noted. Because the certified copy of this document has been filled and the subject matter of the claims under examination is comprised in the priority

document, the priority of the claims under examination to the EPO application has been granted.

Rejections

35 USC 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-15, 33 and 42-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-15 and 33 are confusing. The base claim 6 is directed to a DNA molecule encoding an enzyme that acts as aryltransferase, **or** has an activity within EC 2.7.8, and at the same time the claim is directed to a DNA molecule of SEQ ID NO: 5 encoding the polypeptide sequence of SEQ ID NO: 6 that is disclosed as possessing a single activity, i.e., aryl transferase activity classified as EC2.7.8. Applicants attention is turned to the fact that; aryl transferases are classiffied in EC 2.5. The polypeptide disclosed as having a single enzymatic activity classified in one class may not be claimed as having this very activity or another activity in a different class.

Claims 6, 7 and 42 and dependent claims are rejected for lack of explicit description of hybridization conditions for selection of DNA molecules that hybridize to molecules a) and b) of claims 6 and 42. It is noted that the specification at page 6

exemplifies conditions that may be used for hybridization, but it is not clear which of the several sets of hybridization conditions recited are to be applied to the claimed invention. Secondly, it is not clear whether other hybridization conditions known in the art are included/excluded from the claims. Explicitly quoting hybridization conditions in the claims will overcome this rejection.

Claim 8 is specifically rejected as reciting the phrases term "a sequence which hybridizes selectively", which is not defined in the specification. An indefinite recitation renders the claim indefinite.

Claims 12-14 and 44-45 are rejected as not clear as to whether the host cell is an isolated host cell or a host cell within a living organism. The latter is assumed for examination.

In addition, claim 6 is not clear in recitation "activity within EC2.7.8.-", because it is not clear weather the activity comprises 27 activities belonging to EC 2.7.8.1 – 2.7.8.21 or something else; see the enclosed printout of EC 2.7.8 of IUBMB. **For examination purpose it is assumed that the activity is within EC 2.7.8 and is cobalamin (5'-phosphate) synthase.**

Moreover, claim 42 is not clear in reciting "activity within EC 2.7.1.- , EC 2.7.7.- ", because it is not clear whether the activity comprises EC 2.7.1 and activity EC 2.7.7 or something else. **For examination purpose it is assumed that the activity is EC 2.7.1 and EC 2.7.7 and is cobinamide kinase and cobinamide phosphate guanyl transferase; please note SEQ ID NO: 4 has double activity.**

Claim 15 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential step, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is isolating produced polypeptide, or isolating the synthesized precursor of vitamin B12 or isolating vitamin B12 itself.

Claims 15 and 46 are rejected as confusing, because they seem to be directed to three methods simultaneously; firstly, to a method for producing any polypeptide, secondly to a method of producing any precursor of vitamin B12, and thirdly to a method of producing vitamin B12 itself. Although the three methods share the steps of culturing a host cell of claim 12 or 45, they do not share the step of isolating the produced products. The products are different chemical compounds and require for that matter different methods of isolation. Thus, the three methods may not be practiced together.

35 USC 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

Claims 6-15, 33 and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The base claim 6 is directed to an isolated polynucleotde comprising

(a) the nucleic acid sequence of SEQ ID NO: 5;

(b) a sequence encoding a polypeptide which is a transferase obtainable from a bacterium of the family Mycobacteriaceae, which acts as an aryl transferase or has an activity within EC 2.7.8. and

(1) has an amino acid sequence of SEQ ID NO: 6; or

(2) is a variant of (1) having at least 70%, 75% 80%, 85%, at least 90%, at last 95% sequence identity to the amino acid sequence of SEQ ID NO: 6; or

(3) is a fragment of (1) or (2) , which is at least 150 amino acids in length;

(c) a sequence which is complementary to, or which hybridizes to, a sequence as defined in (a) or (b);

(d) a fragment of a sequence in (a), (b) or (c);

(e) a sequence having 60% identity to a sequence as defined in (a), (b), (c) or, (d); or

(f) a sequence that is degenerated as a result of the genetic code to any one of the sequences as defined in (a) to(e).

Firstly, claim 6 and dependent claims are rejected for new matter. The claims are directed to a large genus of DNA molecules encoding proteins which acts as an aryl

transfrase **or** has an activity from EC 2.7.8. The claims are lacking sufficient description of function of the proteins encoded by the claimed polypeptides. Aryl transferases consists of 71 enzyme activities; see the enclosed print of EC 2.5 of IUBMB. The disclosure teaches that SEQ ID NO: 5 encodes protein of SEQ ID NO: 6 which has a single activity of cobalamin (5'-phosphate) synthase, which is aryl transferase applicants classified as EC 2.7.8. Applicants do not teach any other aryl transferase activity of SEQ ID NO: 6 in the disclosure; see page 14, the table. Thus, the claims directed to broadly claimed aryl transferases contain new matter.

Secondly, claims 42-46 are directed to extremely large and versatile genus of DNA molecule recited as a)-f) of claim 6, and further limited by claim 42, which reads:

The polypeptide according to claim 6 which further comprises:

(a) the nucleic acid sequence of SEQ ID NO: 3;

(b) a sequence encoding a polypeptide which is a transferase obtainable from a bacterium of the family Mycobacteriaceae, which acts as a nucleotidyl **or** phospho transferase or has an activity of EC2.7.1, or EC 2.7.7 and

(1) has an amino acid sequence of SEQ ID NO: 4; or

(2) is a variant of (1) having at least 70%, 75% 80%, 85%, at least 90% at last 95% sequence identity to the amino acid sequence of SEQ ID NO: 4; or

(3) is a fragment of (1) or (2), preferably which is at least 150 amino acids in length;

(c) a sequence which is complementary to, or which hybridizes to, a sequence as defined in (a) or (b);

(d) a fragment of a sequence in (a), (b) or (c);

(e) a sequence having 60% identity to a sequence as defined in (a), (b), (c) or, (d); or

(f) a sequence that is degenerated as a result of the genetic code to any one of the sequences as defined in (a) to (e).

Claim 42 and dependent claims are rejected for new matter. Applicants attention is turned to the fact that SEQ ID NO: 3 encodes SEQ ID NO: 4, which is a protein having two activities; see for example, page 14 of the specification. The activities are phospho transferase **and** nucleotidyl transferase. The disclosure does not teach a protein that has only phospho transferase activity and the disclosure does not teach a protein that has only nucleotidyl transferase activity; this is a new matter.

Furthermore, claims 6, 42 and dependent claims are rejected for lack of written description of any 150 amino acid long fragment of SEQ ID NO: 6 or SEQ ID NO: 4 that has enzymatic activity of cobalamin (5'phosphate) synthase, or phosphor transferase and nucleotidyl transferase. The active center of the claimed enzymes is not disclosed and the function/structure relationship for both enzymes is not taught in the application. Any 150 amino acid long fragment of SEQ ID NOs: 6 and 4 having the enzymatic activity of SEQ ID NO: 4 or 6 is not disclosed.

Furthermore, claims 6 and 42, and dependent claims, are rejected for lack of written description, because their part (d) recites **a fragment of a sequence recited by**

parts (a), (b) and (c) whithout stating what is the structure and function of said fragments.

Furthermore, claims 6 and 42, and dependent claims, are rejected for lack of written description, because their part (e) recites **a sequence having at least 60%** identity to any of sequences sdefined in parts (e) –(d) **without stating what is the function of said sequence.** Applicants' attention is turned to the fact that a sequence that is 60% identical to a sequence that is 70% identical to SEQ ID IDs: 5 or 3 is only 42% identical to SEQ ID NO: 5 or 3, thus probability of having the same activity is not high.

Claim 8 is specifically rejected as directed to any synthase and any transferase. Thus, the claim is lacking specificity in the function of "synthase" or "transferase". Both names are generic and their scope comprises more than tens activities. Synthase is any enzyme which catalyzes a synthesis process; see the enclosed print out of Wikipedia's page. Thus without stating the exact activity applicants disclosed for SEQ ID NO: 6 encoded by SEQ ID NO: 5 the claim suffers from lack of written description.

The method claim 15 is rejected as directed to producing any polypeptide, and any precursor of vitamin B12 or vitamin B12 using the host of claim 12, i.e. the host comprising DNA molecule of claim 6.

1. Applicants disclose SEQ ID NO: 6 that is cobalamin (5'-phosphate) synthase of the invention encoded by SEQ ID NO: 5 may be produced by expressing SEQ ID NO: 5 in a host cell. Thus, SEQ ID NO: 5 may be used for production of SEQ ID NO: 6 cobalamin (5'-phosphate) synthase, but not for production of any polypeptide broadly

claimed by the claim. Moreover, because SEQ ID NO: 6 produces vitamin B12 from adenosyl GDP-cobamide, expressing SEQ ID NO: 5 may be used in production of vitamin B12.

2. However, the disclosure is lacking description of use of SEQ ID NO: 5, and for that matter SEQ ID NO: 6 in producing any precursor of vitamin B12, because SEQ ID NO: 6 does not produce any precursor, but vitamin B12 itself.

3. The disclosure does not teach how to use of any species of extremely large genus of DNA molecules of claim 6 encoding variant of SEQ ID NO: 6 or a 150 amino acid long fragment of SEQ ID NO: 6 or other molecules recited in parts d) to e) of claim 6 for production of any precursor of vitamin B12 or vitamin B12 itself.

Claim 46 is rejected as directed to a method of production of extremely large genus of polypeptides, whose function not stated. The disclosure teaches how to produce, by expressiong SEQ ID NO: 5 and SEQ ID NO: 3 polypeptides of SEQ ID NO: 5 and 4 that have cobalamin (5'-phosphate) synthase activity and cobinamide kinase and cobinamide phosphate guanyl transferase activity and how to use host cells expression them for production of vitamin B12 and its precursor.

Claim 46 is also rejected, because the disclosure does not teach how to use of any species of extremely large genus of DNA molecules of claim 6 and 42 encoding variant of SEQ ID NO: 6/SEQ ID NO: 4 or a 150 amino acid long fragment of SEQ ID NO: 6/SEQ ID NO: 4 or other molecules recited in parts d) to e) of claim 6 and 46 for production of any precursor of vitamin B12 or vitamin B12 itself.

In conclusion, one having skills in the art is not convinced that applicants were in possession of the claimed invention at the time application was filed.

Scope of enablement

Claims 6-15, 33 and 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A) SEQ ID NO: 5 encoding cobalamin (5'-phosphate) synthase of SEQ ID NO: 6;

B) vector comprising SEQ ID NO: 5 as well as a vector that further comprises SEQ ID NO: 3 and SEQ ID NO: 1;

C) host cell comprising said vectors, and methods of recombinantly producing SEQ ID NO: 6 in combination with SEQ ID NO: 4 and SEQ ID NO: 1; and

D) a methods for fermentative production of vitamin B12, and its two precursors adenosil cobinamide phosphate and adenosyl-GDP cobamide,

does not reasonably provide enablement for:

1) any DNA encoding a variant having at least 70%, 75% 80%, 85% and at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 6; or

2) any DNA encoding a fragment of SEQ ID NO: 6 or its variant as in (1) wherein the fragment is, at least 150 amino acids in length;

3) any DNA sequence which is complementary to, or which hybridizes to, a sequence defined in 1) or 2);

4) any fragment of a sequence defined in 1) - 3);

5) any DNA sequence having 60% identity to a sequence as defined in 1)- 4); or

6) any DNA sequence encoding a variant of SEQ ID NO: 4 having at least 70%, 75% 80%, 85%, and at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 4;

7) any DNA encoding fragment of SEQ ID NO: 4 or a fragment of a variant of SEQ ID NO: 4 defined in 6), wherein the fragment is least 150 amino acids in length;

8) any DNA sequence which is complementary to, or which hybridizes to, a sequence as defined in 6) and 7)

9) any fragment of a DNA sequence defined in 6), 7) or 8);

10) any DNA sequence having 60% identity to a sequence as defined in 6)-9);

11) a method of recombinantly producing any polypeptide and

12) a method for fermentatively synthesizing any precursor of vitamin B12.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill

of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

Regarding DNA marked as 1) the nature and breadth of the claimed invention encompasses an extremely large genus DNA molecules that encode any variant of SEQ ID NO: 6 having cobalamin (5'-phosphate) synthase having at least 70% identity to SEQ ID NO: 6; wherein the variant originates from the family of *Mycobacteriace*. The art does not teach enzymes from any Mycobacteriace that are analogous to SEQ ID NO: 6 and have the same activity, and the disclosure does not teach the function/structure relationship for SEQ ID NO: 6 and does not provide examples, or instruction how to modify SEQ ID NO: 6 so as to obtain a variant having at least 70% identity to SEQ ID NO: 6 and still retaining the activity of cobalamin (5'-phosphate) synthase. One having skills in the art is aware that even one change in the amino acid sequence of an enzyme may lead to change of the type of activity of said enzyme or inactivate said enzyme. Providing the only example of the structure of cobalamin (5'-phosphate) synthase from *Mycobacteriace*, i.e. providing SEQ ID NO: 6, does not provide for variants thereof having major structural variation and retaining enzymatic activity. In conclusion, without a further guidance on the part of applicants regarding the structure of the variants, one having skills in the art is left with experimentation that is not routine, has a low probability of success and is undue.

Regarding point 2), because structure/function relationship for the only example of cobalamin (5'-phosphate) synthase from the family of *Mycobacteriace*, i.e., SEQ ID NO: 6, has not been disclosed, the enzymatically active fragment of 150 amino acid of

SEQ ID NO: 6 is not enabled. Finding and making this fragment requires experimentation that is not routine absent any instruction on the part of applicants as to the structure of the catalytic center of the protein. Thus, one having skills in the art is left with experimentation that is undue.

Regarding point 3), because points 1) and 2) require undue experimentation any DNA sequence of point 3) requires an undue experimentation as well.

Regarding point 4) it is not enabled because points 10-3) are not. Even if point 1)-3) were enabled, because the function and structure of the claimed fragment is not recited by the claims, the fragment would not been enabled. One having skills in the art would not know which species of the enormous genus of fragments of DNA molecules of 1) to 3) do constitute the invention. Thus, the skilled artisan is left with experimentation that is has no probability of success; such experimentation is undue.

Regarding point 5) because DNA of points 1) to 4) are not enabled, DNA molecules of point 5) are not enabled as well.

Regarding point 6) the nature and breadth of the claimed invention encompasses an extremely large genus DNA molecules that encode any variant of SEQ ID NO: 4 having both cobinamide kinase and cobinamiede phosphate guanyl transferase activity having at least 70% identity to SEQ ID NO: 4; wherein the variant originates from the family of *Mycobacteriace*. The art does not teach enzymes from any Mycobacteriacae that are analogous to SEQ ID NO: 4 and have the same activity. The disclosure does not teach the function/structure relationship for SEQ ID NO: 4, because the disclosure does not teach the catalytic center/catalytic centers of SEQ iD NO:4. The specification

also fails and does not provide examples, or instruction how to modify SEQ ID NO: 4 so as to obtain a variant having at least 70% identity to SEQ ID NO: 4, and still retaining the activity of cobalamin (5'-phosphate) synthase. One having skills in the art is aware that even one change in the amino acid sequence of an enzyme may lead to change of the type of activity of said enzyme or inactivate said enzyme. Providing the only example of the structure of cobalamin (5'-phosphate) synthase from *Mycobacteriace*, i.e. providing SEQ ID NO: 4, does not provide for variants thereof having major structural variation and retaining both enzymatic activities. In conclusion, without a further guidance on the part of applicants regarding the structure of the variants, one having skills in the art is left with experimentation that is not routine, has a low probability of success and is undue.

Regarding point 7), because structure/function relationship for the only representative of a dual activity of cobinamide kinase and cobinamiede phosphate guanyl transferase from the family of *Mycobacteriace,* i.e., SEQ ID NO: 4, has not been disclosed, the fragment of 150 amino acid of SEQ ID NO: 4 that is enzymatically active and possesses both activities is not enabled. Finding and making this fragment requires experimentation that is not routine absent any instruction on the part of applicants as to the structure of the catalytic ceter/centers of the protein. Thus, one having skills in the art is left with experimentation that is undue.

Regarding point 8), because points 6) and 7) require undue experimentation any DNA sequence of point 3) requires an undue experimentation as well.

Regarding point 9) even if point 6)-8) were enabled, because the function and structure of the claimed DNA fragment is not recited by the claims, the fragment is not enabled. One having skills in the art would not know which species of the enormous genus of fragments of DNA molecules 7) to 8) do constitute the invention. Thus, the skilled artisan is left with experimentation that has no probability of success; such experimentation is undue.

Regarding point 10) because DNA molecules of points 6) to 9) are not enabled, DNA molecules of point 10) are not enabled as well.

Regarding point 11, claims 15 and 46 are directed to production of any polypeptide by the host cells comprising DNA molecule of claim 6 or claim 43. A indicated above, although the disclosure is enabling for an isolated host cell transformed with a vector comprising SEQ ID NO: 5, as well as a vector that further comprises SEQ ID NO: 3 and SEQ ID NO: 1, because DNA molecules listed in this rejection as 1-10 are not enabled, vectors and isolated host cells comprising DNA molecules 1-10 are not enabled as well. For that matter, recombinant production of an extremely large and versatile genus of polypeptides encoded by vectors comprising DNA molecules 1)-10) is not enabled, i.e. it would require experimentation with a very low probability of success or without a success, therefore undue.

Claims 15 and 46 are also rejected because although the disclosure provides for methods for fermentative production of vitamin B12, and its two precursors adenosil cobinamide phosphate and adenosyl-GDP cobamide, by isolated host cells containing vectors comprising SEQ ID NO: 5, or SEQ ID NO: 5 and 3, or SEQ ID NO: 5, 3, and 1,

the disclosure is not enabling for production of any precursor of vitamin B12 by the vector that contains SEQ ID NO: 5, or SEQ ID NO: 5 and SEQ ID NO: 3. SEQ ID NO: 5 does not provide of synthesis of any precursor of vitamin B12. In addition, a combination of SEQ ID NO: 5 and 3 does not provide for production of other precursors, i.e., cobyrinic a, c,diamide that is a substrate for SEQ ID NO: 4, or cobyrinic acid that is a substrate for SEQ ID NO: 2. Thus the precursor that is to be produced must be explicitly stated in the claims.

In summary, without a further guidance as on the part applicants, as explained above, the experimentation left to those skilled in the are is not routine, has a low probability of success and thus undue.

Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or

Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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